

invention was made to use the teachings of the cited secondary references, with a reasonable expectation of success, for washing crystals, or an oily form of reduced coenzyme Q₁₀, because it is within the scope of the art to optimize the conditions and achieve the claimed results through routine experimentation according to the Examiner. The applicants steadfastly disagree with the Examiner's conclusion in the circumstances which prevail here!

According to the invention of Claims 1-19, reduced coenzyme Q₁₀ is purified by washing crystals and/or oil of reduced coenzyme Q₁₀ with a water-soluble organic solvent or a mixed solvent composed of a water-soluble organic solvent and water and thereby removing a water-soluble impurity, that is, a reducing agent and an impurity derived from a reducing agent. In a large-scale production, it is essential to conduct a simple and easy purification of the product. Therefore, purification without column chromatography is desirable. The Claim 1-19 invention enables such purification by utilizing a water-soluble organic solvent.

In Example 1, of the invention disclosure, crystals of reduced coenzyme Q₁₀ (containing 3.2% of L-ascorbic acid and 0.36% of oxalic acid) obtained in Production Example 1 were each washed with aqueous ethanol solutions (mixtures of ethanol and water). As shown in Table 1, after washing, contents of L-ascorbic acid were 0.07% or less and contents of oxalic acid were 0.05% or less. On the other hand, in Comparative Example 1 where water was used for washing, content of L-ascorbic acid was 0.18% and content of oxalic acid was 0.15%, and recovery percentage was only 97%. The Examiner says that it is desirable to use suitable solvents in which impurities get dissolved and the selection of a solvent depends on the solubility of the impurities. In this regard, it would seem normal to use water for washing in order to remove water-soluble impurities from

reduced coenzyme Q₁₀ crystals which are highly insoluble to water. However, Table 1 shows the results to the contrary. In Production Example 2, sodium hyposulfite was used as a reducing agent. When aqueous ethanol solution was used for washing of crystals (Example 5), content of impurities was 0.08%. On the other hand, when water was used (Comparative Example 3), the content of impurities was 0.18%, crystals adhered to the wall surface and it was very hard to carry out the discharge operation. It is unacceptable to spend too much time for purification since reduced coenzyme Q₁₀ is easily oxidized. Thus, as shown above, it is an unexpected effect that water-soluble organic solvents are most effective for removing water soluble impurities.

The Examiner contends that the Kijima et al ('660) reference teaches washing of crystals with diethyl ether in Example 1. Applicants respectfully request careful reconsideration of that reference. In Example 1 of Kijima et al ('660), the reaction mixture contained silica-alumina (col. 4, lines 40 to 43). The filtration was carried out to remove the solid material, namely silica-alumina. After the filtration, the solids were washed with diethyl ether to collect a desired product which adhered to the surface of silica-alumina and to increase the yield. Such washing is a common procedure and a person skilled in the art would readily understand that the procedure is not for removing impurities from crystals of a desired product.

After the washing procedure in Kijima et al ('660), the filtrate and the washing liquor were collected, washed with water and then with aqueous solution of sodium hydroxide, and concentrated to obtain a light yellow oily product. The crude product was purified by silica gel column chromatography (col. 4, lines 51 to 59). The reference explicitly teaches that the filtrate was washed with water, and the purification of the crude

product was carried out by column chromatography. The procedure does not include a washing of crystals or oil of a desired product with a water-soluble organic solvent.

Regarding the Kijima et al ('573) reference, it only teaches that in Example 3 the filtrate was washed with water and then with a weak-caustic soda aqueous solution. The procedure does not include a washing of crystals or oil of a desired product with a water-soluble organic solvent.

Regarding the Morita et al reference, it teaches in Example 1, that the filtrate was washed with methanolic aqueous sodium hydroxide solution and then with aqueous methanol solution (col. 4, lines 31 to 36). The procedure taught is for washing of filtrate liquor, namely a solution of a desired product. The reference does not teach a washing of crystals or oil of a desired product with a water-soluble organic solvent.

It will thus be clearly understood, as discussed above, that the secondary references only disclose washing of a solution containing organic solvents. They do not teach washing crystals or an oily form of a product with a water-soluble organic solvent or a mixture of a water-soluble organic solvent and water. First of all, none of the secondary references disclose purification of reduced coenzyme Q₁₀. Therefore, it cannot be determined from the teachings of the references which solvent is most appropriate for removing a reducing agent contained in reduced coenzyme Q₁₀. Furthermore, it would be entirely unpredictable from the teaching of any of the secondary references to conclude that a water-soluble organic solvent is effective for removing water-soluble impurities and improving the yield and is more convenient to carry out the discharge operation than water.

As such, applicants submit that the claimed invention would plainly not have been rendered obvious over Merck & Co., Inc in combination with Kijima et al ('660), Kijima et al ('573) or Morita et al. As such, Claims 1-19 should be allowed.

Respectfully submitted,

/Richard G. Lione/

Richard G. Lione

Reg. No. 19,795

Attorney for Applicant(s)

BRINKS HOFER GILSON & LIONE
P.O. Box 10395
Chicago, Illinois 60610
(312) 321-4200